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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/476,485	12/30/1999	M. Gabriella Colucci	108.236.119	7906

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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	**PAPER NUMBER**
1644	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/476,485	COLUCCI ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73-80 and 84* is/are rejected.

7)☒ Claim(s) *81-83* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 07/29/04 is acknowledged.

Claims 73-84 are pending.

In view of the amendment, filed 07/29/04 the following rejections remain:

2. The following is a quotation of the second paragraph of 35 U.S.C. 112.
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 73, 75-80 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The recitation of "hybridizing under stringent conditions" in claim 73 is ambiguous. Although the specification discloses on page 21 line 23 general parameters for calculating such conditions, in the absence of a clear definition of the metes and bounds of this phrase it is unclear which conditions are actually claimed.

It is suggested that Applicant amend the claims to recite a particular set of hybridization and wash conditions to overcome this rejection.

Applicant's arguments, filed 07/29/04 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) one skill in the art would be readily able to ascertain the meaning of the phrase " hybridized under stringent conditions"; (ii) recently issued US Patents include claims to nucleic acids which "hybridize under stringent conditions".

Contrary to Applicant's assertions it is the Examiner position that in the absence of a clear definition of the metes and bounds of general term " hybridizing under stringent conditions' i.e. a particular set of hybridization and wash conditions, it is unclear which conditions are actually claimed.

Also, it is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991). Moreover, as stated In re Borkowski, 505 F2d 713,718,184

USPQ29,33 (CCPA 1974), "The Paten Office must have the flexibility to reconside and correct prior decisions that may find to have been in error". In a similar context, the court in Fessenden v.Coe, 38 USPQ 516,521 (CADC 1938) stated that '[t]wo wrongs cannot make a right."

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 73-80 and 84 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is D1 –FRIL (SEQ ID NO:2) from *Dolichos lab lab* or PV-FRIL (SEQ ID NO:6) from *Phaseolus vulgaris* or Yam-FRIL (SEQ ID NO: 8) from *Sphenostylis stenocarpa* that can be used to preserve progenitor cells does not reasonably provide enablement for a pharmaceutical formulation comprising protein, wherein said protein is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7, claimed in claims 73 or a pharmaceutical formulation comprising a protein s, wherein said protein has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, claimed in claims 74 and 84 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims for the same reasons set forth in the previous Office Action, mailed on 04/29/04 .

Applicant's arguments, filed 07/29/04 have been fully considered, but have not been found convincing.

Applicant asserts that : (i) the application teaches the method used to isolate and purify three different FRIL protein (ii) the amended claims include both structure and functional limitation . i.e. binds to a normally glycosylated FLT3 receptor and preserving hematopoietic progenitor cells.

Contrary to Applicant's assertion, as was stated in the previous Office Action, the claims as written encompass the genus of a FRIL family members. The genus encompasses peptides wherein such peptides have numerous differences in amino acid sequences. Applicant discloses only FRIL from *Dolichos lab lab that* is D1 –FRIL (SEQ ID No.2), or PV-FRIL (SEQ ID No.6) from *Phaseolus vulgaris* or Yam-FRIL (SEQ ID No. 8) from *Sphenostylis stenocarpa* in the instant specification (see page 56, line 3-9 ; page 83, line 25-30, and page 121, lines 5-11 . Applicant only disclosed a pharmaceutical composition comprising of D1 –FRIL (SEQ ID

NO:2) or PV-FRIL (SEQ ID NO:6) or Yam-FRIL (SEQ ID NO: 8) that have a progenitor cell preservation activity (see Examples 1, 5, 10, 11 and 22 in particular).

It is noted that amendment claims have added the function of the peptide. However, these amendments do not obviate the issues of enablement rejection set forth in the previous office action of on 04/29/04. Applicant is relying upon certain biological activities and the disclosure of a three species to support an entire genus. The claims as written encompass a broad genus of polypeptides with an unlimited number of possibilities with regard to the length of the polypeptide sequence. Further, the enablement issues of making the protein still remain because the specification does not teach and provide sufficient guidance as to which amino acid of SEQ ID NOs : 2, 6 and 8 would have been altered such that the resultant polypeptide would have retained the function of preservation of progenitor cell activity or reducing a progenitor cell depleting activity. The disclosure of SEQ ID NOS: 2, 6 and 8 cannot support the entire genus of FRIL family of progenitor cell preservation factors derived from plant lectins. In addition, Moore (US Patent 6,084,060) teaches that whether plant lectins act on mammalian cells via de novo means, or simply mimic their functional mammalian homolog is not yet know. No lectin has been successfully developed as human therapeutics (see column 2, lines 24-30 in particular). Therefore, absent the ability to predict which of these peptides would function as claimed, and given the lack of data on regions critical for activity, for one of skill in the art to practice the invention as claimed would require a level of experimentation that is excessive and undue.

Since the instant fact pattern fails to indicate that representative number of structurally related compounds is disclosed, the artisan would not know the identity of a reasonable number of representative compounds falling within the scope of the instant claims and consequently would not know how to make them. An assay for *finding* a product is not equivalent to a positive recitation of *how to make* a product.

Applicant has not taught how to make and/or use a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7, or a pharmaceutical formulation comprising a FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8 that have progenitor cell preservation activity or reduces a progenitor cell depleting activity.

It is known in the art that even single amino acid changes or differences in a proteins amino acid sequence can have dramatic effects on the protein's function. For example, Mikayama et al. (PNAS, 1993. 90: 10056-10060) teach that the human glycosylation factor (GIF) protein differs from human macrophage migration inhibitory factor (MIF) by a single amino acid residue (see

Figure 1 in particular). Yet, Mikayama et al. further teach that GIF is unable to carry out the function of MIF and MIF does not demonstrate GIF activity (see Abstract in particular).

Applicant is relying upon certain biological activities and the disclosure of a limited number of species to support an entire genus. It is well known that minor structural differences among even structurally related compounds or compositions can result in substantially different biology, expression, and pharmacology of proteins. Therefore, structurally unrelated any FRIL encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7, or any FRIL family member of progenitor cell preservation factors, wherein FRIL has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8, would be expected to have greater differences in their activities.

Since the amino acid sequence of a polypeptide determines its structure and functional properties, predictability of which changes can be tolerated in a polypeptide's amino acid sequence and still retain similar functionality (e.g. binding of FRIL to a normally glycosylated FLT3 receptor, as stressed by Applicant is essential for the invention, see page 25, line 3-5 in particular) requires a knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification) and detailed knowledge of the ways in which a polypeptide's structure relates to it's functional usefulness. However, the problem of predicting polypeptide structure from mere sequence data of a single amino acid sequence and in turn utilizing predicted structural determinations to ascertain functional aspects the peptides and finally, what changes can be tolerated with respect thereto is complex and well outside the realm of routing experimentation.

Since the amino acid sequence of a polypeptide determined its structural and functional properties, predictability of which fragments will retain functionality requires knowledge of, and guidance with regard to, which amino acids in the polypeptide's sequence contribute to its structure, and therefore, function. The problem of predicting which fragments or derivatives of a protein will retain functionality and which will not is complex and well outside the realm of routine experimentation. Because of the lack of sufficient guidance and predictability in determining which structures would lead to functional proteins or peptides with the desired properties and that the relationship between the sequence of a peptide and it's tertiary structure (i.e. its activity) was not well understood and was not predictable (e.g. see Ngo et al, in The Protein Folding Problem and Tertiary Structure Prediction, 1994. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495.); it would require an undue amount of experimentation for one of skill in the art to arrive at the breadth of proteins encompassed by the claimed invention.

In view of this unpredictability the skilled artisan would not reasonably expect a polypeptide having anything less than 100% identity over the full length of SEQ ID NO:2, 6 and 8 to *share the same function* as D1 –FRIL (SEQ ID NO:2) or PV-FRIL (SEQ ID NO:6) or Yam-FRIL (SEQ ID NO: 8) that have a progenitor cell preservation activity reduces a progenitor cell depleting activity.

Similarly, the fact that two nucleic acid sequences will hybridize under moderate or stringent conditions does not in and of itself require that the two sequences share any functional activity. Thus the same observations apply to the recitation of " a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7", claimed in claims 73 as were noted above with respect to "percent identity" language. Further, it was well known in the art at the time the invention was made that hybridization could occur between two sequence based upon short stretches of 100% identity. Thus a great deal of sequence variability *with respect to the full-length nucleic acid* is possible and in the absence of a clear recitation that the identity is over the full length of SEQ ID NOs:1 5 and 7 , the claim reads on subsequences and would be viewed by the skilled artisan as been even less likely to encode a polypeptide with the same function as FRIL proteins encoded by SEQ ID NOs:2 , 6 and 8. Finally, hybridization under conditions other than high stringency would be expected to permit a great deal of variation between the two hybridizing sequences, making it even more unpredictable that the two sequences would share the same function. Thus as for the recitation of percent identity, hybridization language in the absence of *a testable function* and limitations regarding both the *hybridization conditions* and the *sequence length over which the hybridization takes place*; does not allow the skilled artisan to make and use the hybridizing nucleic acids commensurate in scope with the instant claims without undue experimentation.

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use claimed a pharmaceutical formulation comprising a protein , wherein said protein is encoded by a nucleic acid molecule that hybridizes under stringent conditions to a nucleic acid having a nucleotide sequence complementary to a nucleotide sequence of SEQ ID NOs: 1, 5 and 7, or a pharmaceutical formulation comprising a protein wherein said protein has at least 95 % amino acid sequence identity to amino acid sequences of SEQ ID NOs : 2, 6 and 8 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

6. Claims 81-83 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

7. No claim is allowed

8. **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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